(55,56,57) where the polyethylene glycol can be attached to residues of lysine or arginine (58,59,60).

The following concerns immunogenicity. For drugs that are antibodies, enzymes, cytokines, and hormones, what is desired is that it is not immunogenic. In other words, what is desired for these particular drugs is that the drug does not provoke an immune response against the drug itself. But in striking contrast, for drugs that are vaccines, the purpose of the drug is to stimulate immune response against the drug itself, and (hopefully) also to stimulate an immune response against the infecting agent or tumor that contains a similar or identical polypeptide sequence. Knowledge of the amino acids is needed for understanding all of the above issues.

IV. ANIMAL MODELS

a. Introduction

Regulatory approval for drugs requires data on safety and efficacy in animals. While data on safety can be acquired from studies on mice, rats, rabbits, dogs, and primates, data on efficacy can only be acquired where there is an available animal model of the disorder in question. Where the goal of the drug is to enhance wound healing, it is easy to find a suitable animal model (all that is needed is to surgically remove a circle of skin from the animal). However, where the goal of the drug is to treat diseases such as cancer, immune diseases, or infections, there is a need to find an appropriate animal model.

While rodents spontaneously develop various cancers, it is not practical to acquire a group of rodents with the same type of cancer, and at the same stage of the cancer, at the same time. The array of tumors that occur spontaneously in rats has been exhaustively documented (61,62).

Separate animal models are available for various types of cancer. Marks (63) identified sources of various animal cancer models. Nandan and Yang (64) Kuperwasser

[55] Ramos EL. Preclinical and clinical development of pegylated interferon-lambda 1 in chronic hepatitis C. *J Interferon Cytokine Res*. 2010;30:591–595.

[56] Hershfield MS, Roberts LJ. 2nd, Ganson NJ, et al. Treating gout with pegloticase, a PEGylated urate oxidase, provides insight into the importance of uric acid as an antioxidant in vivo. *Proc Natl Acad Sci USA*. 2010;107:14351–14356.

[57] Fishburn CS. The pharmacology of PEGylation: balancing PD with PK to generate novel therapeutics. *J Pharm Sci*. 2008;97:4167–4183.

[58] Lee H, Park TG. Preparation and characterization of mono-PEGylated epidermal growth factor: evaluation of in vitro biologic activity. *Pharm Res*. 2002;19:845–851.

[59] Veronese F, Sartore L, Orsolini P, Deghenghi R. U.S. Pat. No. 5,286,637.

[60] Gauthier MA, Klok HA. Arginine-specific modification of proteins with polyethylene glycol. *Biomacromolecules*. 2011;12:482–493.

[61] Son WC, Bell D, Taylor I, Mowat V. Profile of early occurring spontaneous tumors in Han Wistar rats. *Toxicol Pathol*. 2010;38:292–296.

[62] Bomhard E. Frequency of spontaneous tumors in Wistar rats in 30-months studies. *Exp Toxicol Pathol*. 1992;44:381–392.

[63] Marks C. Mouse Models of Human Cancers Consortium (MMHCC) from the NCI. *Dis Model Mech*. 2009;2:111.

[64] Nandan MO, Yang VW. Genetic and chemical models of colorectal cancer in mice. *Curr Colorectal Cancer Rep*. 2010;6:51–59.